European Heart Journal (2014) **35**, 2672–2684
doi:10.1093/eurheartj/ehu162

CLINICAL RESEARCH
TAVI

Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study

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Received 17 September 2013; revised 17 March 2014; accepted 19 March 2014; online publish-ahead-of-print 28 March 2014

Aim Transcatheter aortic valve implantation has become an alternative to surgery in higher risk patients with symptomatic aortic stenosis. The aim of the ADVANCE study was to evaluate outcomes following implantation of a self-expanding transcatheter aortic valve system in a fully monitored, multi-centre 'real-world' patient population in highly experienced centres.

Methods and results Patients with severe aortic stenosis at a higher surgical risk in whom implantation of the CoreValve System was decided by the Heart Team were included. Endpoints were a composite of major adverse cardiovascular and cerebrovascular events (MACCE; all-cause mortality, myocardial infarction, stroke, or reintervention) and mortality at 30 days and 1 year. Endpoint-related events were independently adjudicated based on Valve Academic Research Consortium definitions. A total of 1015 patients [mean logistic EuroSCORE 19.4 ± 12.3% [median (Q1,Q3), 16.0% (10.3, 25.3%)], age 81 ± 6 years] were enrolled. Implantation of the CoreValve System led to a significant improvement in haemodynamics and an increase in the effective aortic valve orifice area. At 30 days, the MACCE rate was 8.0% (95% CI: 6.3–9.7%), all-cause mortality was 4.5% (3.2–5.8%), cardiovascular mortality was 3.4% (2.3–4.6%), and the rate of stroke was 3.0% (2.0–4.1%). The life-threatening or disabling bleeding rate was 4.0% (2.8–6.3%). The 12-month rates of MACCE, all-cause mortality, cardiovascular mortality, and stroke were 21.2% (18.4–24.1%), 17.9% (15.2–20.5%), 11.7% (9.4–14.1%), and 4.5% (2.9–6.1%), respectively. The 12-month rates of all-cause mortality were 11.1, 16.5, and 23.6% among patients with a logistic EuroSCORE ≤10%, EuroSCORE 10–20%, and EuroSCORE >20% ($P < 0.05$), respectively.

Conclusion The ADVANCE study demonstrates the safety and effectiveness of the CoreValve System with low mortality and stroke rates in higher risk real-world patients with severe aortic stenosis.

Keywords Aortic stenosis • Transcatheter aortic valve implantation • CoreValve • Valvuloplasty • Mortality

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Introduction

Despite advances in cardiac surgery and low mortality rates after conventional aortic valve replacement, up to one-third of patients with symptomatic aortic stenosis are not considered for surgical valve replacement, often due to frailty and co-morbidities.[1,2]

Transcatheter aortic valve implantation (TAVI) enables treatment of aortic stenosis without open heart surgery.[3–15] Recently, balloon-expandable TAVI has been shown to be superior to the standard medical therapy for inoperable patients and to be non-inferior to surgical aortic valve replacement in high-risk patients with aortic stenosis.[16–19] In addition, recent registries including FRANCE 2 suggest that TAVI using the self-expanding CoreValve System (Medtronic, Inc., Minneapolis, MN, USA) appears to represent an alternative option for the treatment of aortic stenosis in elderly high-risk patients.[10,11,13,20] However, most of the published TAVI registries lack rigorous monitoring and central adjudication of events, which might lead to an underreporting of events. In addition, some of the centres contributed data despite the fact that they were still proctored or on the learning curve.[10,11,13,20] Therefore, the CoreValve ADVANCE study was designed to evaluate clinical outcomes following TAVI using the CoreValve System at experienced implanting centres, with adverse event adjudication by an independent Clinical Events Committee according to the original definitions of the Valve Academic Research Consortium (VARC-1).[21]

Methods

Patients

ADVANCE (trial registration can be found at http://clinicaltrials.gov/NCT01074658) is a prospective, multi-centre, fully monitored, non-randomized study that included 44 sites in 12 countries where the CoreValve System was commercially available. Centres were required to have an on-site multidisciplinary 'Heart Team' comprising at least one TAVI-experienced interventional cardiologist and one cardiothoracic surgeon. In addition, the team had to be independent from proctoring, and have a total TAVI experience of at least 40 cases before joining the ADVANCE study.

The ethics committee at each study centre approved the investigational protocol. The study was conducted in adherence to the Declaration of Helsinki and all the patients were informed of the nature of the study and provided a signed consent form at least 1 day prior to the CoreValve implantation procedure. Patients were assessed at 30 days and 12 months following the procedure.

Real-world patients with severe symptomatic aortic stenosis, who were considered inoperable or at a higher risk for conventional aortic valve replacement and were anatomically acceptable candidates for elective treatment with the CoreValve System, were considered for enrolment. Only patients currently participating in another trial, patients who were unwilling or unable (e.g. patients with dementia or those not able to comprehend the scope of their participation in the study) to provide written informed consent were excluded from study participation prior to the TAVI procedure.

Patient enrolment continued until ~1000 consented patients had undergone an implantation procedure.

Study devices and procedures

Detailed device description and implant procedures for the CoreValve System have been previously described.[3,5,22] The method used to assess the aortic annulus and the size of the access vessels was left to the discretion of the operator. Implantations were performed with the 18F delivery catheter, later improved by the AccuTrak Stability Layer (Medtronic). Two valve sizes (26 and 29 mm) were available for an aortic valve annulus size ranging from 20 to 27 mm. The location (transfemoral, direct aortic, and subclavian) and the type of access (surgical cut down or completely percutaneously) and the type of anaesthesia (general or deep sedation) were left to the discretion of the Heart Team. Aortic regurgitation was assessed by angiography after implantation while still in the procedure room. Each centre managed patients with residual aortic regurgitation (AR) following TAVI per standard local procedures, which could include snaring, post-dilatation and implantation of a second CoreValve as a valve in the valve procedure.

Aortic regurgitation after implantation of the CoreValve System was assessed by transthoracic echocardiography and classified by a local, experienced echocardiographer according to the recommendation of the European Association of Echocardiography (none, mild, moderate, or severe).[23] Medications, including antiplatelet and anticoagulation therapies, were administered based on hospital-specific procedures.

Study endpoints

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) at 30 days post-procedure defined as a composite of all-cause mortality, myocardial infarction (Q-wave and non-Q-wave), stroke, or reintervention. Secondary safety endpoints included the individual components of MACCE; cardiovascular mortality, the composite of stroke and all-cause mortality; and bleeding at 30 days and 12 months. Secondary endpoints included procedural and device success and New York Heart Association (NYHA) functional class at discharge, 30 days and 12 months. Device success is defined as meeting the following criteria; successful device delivery, stable device placement, intact retrieval of the delivery catheter, and successful device function as assessed immediately post-procedure by angiography including non-compromised flow in the coronary arteries, no device migration, and a mean AV gradient <15 mmHg as determined invasively with $\leq$ grade 2 AR. Procedure success is defined as device success in the absence of in-hospital MACCE.

Surgical risk factors

The surgical risk for each patient was evaluated using the Society of Thoracic Surgeons (STS) Score and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE). Both instruments are reported on a scale from 0 to 100% with higher values associated with a greater risk. To determine whether patients at low- and high-risk (according to the logistic EuroSCORE) benefit equally from the TAVI procedure, we divided the patient population into three groups: logistic EuroSCORE $\leq$10% (group 1), $>$10% but $\leq$20% (group 2) and $>$20% (group 3).

Study oversight and data management

The study Steering Committee and the sponsor (Medtronic) designed the protocol and case report forms. Source documentation for all the patients was fully monitored, and compared with the database. All discrepancies were resolved prior to locking the database for this report. All primary endpoint events were adjudicated by an independent Clinical Events Committee comprising TAVI-experienced interventional cardiologists and a cardiac surgeon using the VARC-1 definitions.[21] All cerebrovascular events were adjudicated by an independent neurologist utilizing all available relevant source documents including neuroimaging and systematic National Institute of Health Stroke Scale assessments. A core laboratory (Cardialysis, Rotterdam, The Netherlands) performed systematic review and assessment of ECGs and procedural angiograms. Data were recorded

on a standardized electronic case report form and sent to a central database (Merge, Chicago, IL, USA) over the Internet.

Statistical analysis

Categorical variables are reported as counts and percentages with asymptotic 95% confidence intervals (CIs) and group comparisons are based on logistic regression models. Continuous variables are reported as means and standard deviations with 95% CI and group comparisons based on general linear models. The logistic EuroSCORE and STS mortality are summarized using medians and inter-quartile ranges [quartile 1 (Q1) and quartile 3 (Q3)], and comparisons are based on non-parametric general linear models. Outcomes were calculated using Kaplan–Meier survival analysis and the log-rank test was used to test for differences across and between groups. Group pairwise comparison *P*-values are presented, if the overall *P*-values for differences across all three groups are <0.05. Freedom-from-event curves were generated using the Kaplan–Meier method, and the log-rank test was used for comparisons across the EuroSCORE, AR, and PVL groups. For subjects without an event, the date of censoring was the latest date of all follow-up visits (including study exit) and events (including death).

Univariable Cox regression models were used to evaluate potential predictors of 12-month mortality. Statistically significant variables with a *P*-value ≤ 0.05 from the univariable analysis were included in the multivariable model. Hazard ratios with two-sided 95% CIs were calculated. All tests were two-sided; however, *P*-values were not adjusted for multiple comparisons. For interpretation purposes, the pairwise comparison *P*-values should be compared with a Bonferroni-adjusted level of $0.05/3 = 0.017$. All analyses were performed using the SAS software (Version 9.2, Cary, NC, USA).

Results

Patients

From March 2010 to July 2011, 1015 patients were enrolled in the ADVANCE study (see Supplementary material online, *Figure*). The mean age was 81.1 ± 6.4 years (range 51–96 years) and 51% were female (*Table 1*). The baseline peak and mean aortic valve gradients were 75.9 ± 25.1 and 45.6 ± 15.5 mmHg, respectively, and the mean aortic valve area was 0.7 ± 0.3 cm^2. The median (Q1, Q3) logistic EuroSCORE was 16.0% (10.3, 25.3%) and the median (Q1, Q3) STS score was 5.3% (3.6, 7.8%).

Procedural characteristics

Of the 996 patients implanted, 874 (87.8%) underwent implantation of the CoreValve System via the femoral approach, and 6 patients (0.6%) were implanted via the iliac approach for a total iliofemoral rate of 88.4%. The subclavian approach was used in 95 patients (9.5%) and the direct aortic approach in 21 (2.1%). Pre-TAVI balloon valvuloplasty was performed in 906 patients (91.0%). General anaesthesia was used in 445 of cases (44.7%), and a surgical cut down was performed to expose the access vessels in 6.3%.The procedural outcomes are reported in *Table 2*.

Primary endpoint

The rate of the primary endpoint of MACCE was 8.0% (95% CI: 6.3–9.7%) at 30 days and 21.2% (18.4–24.1%) at 12 months (*Tables 3* and *4*; *Figure 1A*).

Secondary endpoints

Tables 3 and *4* show all major safety endpoints at 30 days and 12 months. The rate of all-cause mortality was 4.5% (3.2–5.8%) and 17.9% (15.2–20.5%) at 30 days and 12 months (*Figure 1B*); cardiovascular mortality was 3.4% (2.3–4.6%) and 11.7% (9.4–14.1%) (*Figure 1C*; *Tables 3* and *4*), VARC-defined major bleeding rates were 9.7 and 11.2%, major vascular complications rates were 10.9 and 12.0%, and the rates of acute kidney injury (stage III)[22] were 0.4 and 0.6%. The overall rate of stroke was 3.0% (2.0–4.1%) at 30 days and 4.5% (2.9, 6.1%) at 12 months (*Figure 1D*; *Tables 3* and *4*); and the rates of major stroke were 1.2% (0.5–1.9%) and 2.2% (1.1–3.3%) for the same time periods, respectively. A new permanent pacemaker was implanted in 26.3% (23.5–29.1%) of patients at 30 days and 29.2% (25.6–32.7%) through 12-month follow-up.

Valve assessment

The CoreValve System was effective at reducing the mean aortic valve gradient from 45.6 ± 15.5 mmHg at baseline to 9.8 ± 5.4 mmHg at discharge, 9.3 ± 4.8 mmHg at 30 days and 9.5 ± 5.2 mmHg at 12 months. This was associated with an increase in an effective orifice area from 0.7 ± 0.3 cm^2 at baseline to 1.7 ± 0.5 cm^2 at discharge, 1.7 ± 0.5 cm^2 at 30 days and 1.7 ± 0.5 cm^2 at 12 months.

At discharge, 897 patients had echocardiographic measurements of *total* AR or had died (*Figure 2A*). There was no AR in 172 patients (19.2%); mild AR was present in 561 patients (62.5%), moderate AR in 138 (15.4%), severe AR in 2 (0.2%), and 24 patients had died (2.7%). For the 840 patients alive and with paravalvular AR (PVR) measurements at discharge (*Figure 2B*), there was no PVR in 206 patients (23.8%); mild PVR was present in 504 patients (58.3%), moderate PVR in 128 (14.8%), severe PVR in 2 (0.2%), and 25 patients had died (2.9%). In addition, there were 422 patients with paired AR data at discharge, 1 month, 6 months, and 12 months; and 352 patients with paired PVR data at these time points. Among patients with paired data, the proportion of patients with moderate total AR remained fairly constant ranging from 13.7% at discharge; 15.4% at 1 month, 13.3% at 6 months, and 13.5% at 12 months. To determine change in total AR, there were 561 patients with paired total AR data at discharge and at 12 months. Of these, 138 (24.6%) improved, 337 (60.1%) had no change, and 86 (15.3%) worsened. To determine change in PVR, there were 510 patients with paired PVR data at discharge and at 12 months. Of these, 136 (26.7%) improved, 289 (56.7%) had no change, and 85 (16.7%) worsened.

Clinical symptoms

At baseline, 35 patients (3.5%) had NYHA class I symptoms, 168 patients (16.9%) were in NYHA class II, 672 patients (67.4%) in NYHA class III, and 122 patients (12.2%) in NYHA class IV. At 30 days, 84.2% of the followed patients were in NYHA class I or II and 86.9% at 12 months.

Pre-specified clinical outcomes by logistic EuroSCORE

The higher logistic EuroSCORE in group 3 was driven by the advanced age of the patients and the presence of more co-morbidities when compared with group 1 (*Table 1*). At 30 days, overall survival and cardiovascular survival did not differ among the three patient groups (*Figure 1B* and *C*; *Table 3*); however, at 12

Table 1 Baseline characteristics for all patients and by EuroSCORE[a]

Assessment	All patients (n = 1015)	EuroSCORE[b] ≤10% (n = 232)	EuroSCORE >10–20% (n = 412)	EuroSCORE >20% (n = 369)	Overall *P*-value	*P*-value[c]	*P*-value[d]	*P*-value[e]
Age, years	81.1 ± 6.4 (80.7, 81.5)	77.6 ± 6.9	81.7 ± 6.1	82.7 ± 5.7	<0.001	<0.001	<0.001	0.023
STS mortality[f], %[median (Q1, Q3)]	5.3 (1014) (3.6, 7.8)	3.2 (2.4, 4.6)	5.1 (3.5, 7.2)	7.1 (368) (5.0, 10.1)	<0.001	<0.001	<0.001	<0.001
Logistic EuroSCORE, % [median (Q1, Q3)]	16.0 (1013) (10.3, 25.3)	7.9 (5.8, 9.0)	14.7 (12.3, 17.0)	29.0 (24.4, 37.2)	<0.001	<0.001	<0.001	<0.001
New York Heart Association class III or IV	794/997 (79.6) (77.1, 82.1)	174/226 (77.0)	311/406 (76.6)	307/363 (84.6)	0.013	0.911	0.021	0.006
Diabetes mellitus	314/1003 (31.3) (28.4, 34.2)	81/231 (35.1)	134/405 (33.1)	99/365 (27.1)	0.08	–	–	–
Coronary artery disease	585/1012 (57.8) (54.8, 60.8)	114/231 (49.4)	226/411 (55.0)	244/368 (66.3)	<0.001	0.170	<0.001	0.001
Previous myocardial infarction	162/990 (16.4) (14.1, 18.7)	21/228 (9.2)	58/402 (14.4)	81/358 (22.6)	<0.001	0.059	<0.001	0.004
Previous percutaneous coronary intervention	316/1004 (31.5) (28.6, 34.3)	62/229 (27.1)	120/409 (29.3)	133/364 (36.5)	0.027	0.543	0.017	0.034
Previous median sternotomy	176/1011 (17.4) (15.1, 19.7)	18/231 (7.8)	53 (12.9)	103/366 (28.1)	<0.001	0.051	<0.001	<0.001
Previous aortic valve intervention	44/1013 (4.3) (3.1, 5.6)	6/231 (2.6)	12/411 (2.9)	25 (6.8)	0.014	0.812	0.030	0.014
Previous coronary artery bypass grafting	217/1011 (21.5) (18.9, 24.0)	17/231 (7.4)	70/410 (17.1)	128/368 (34.8)	<0.001	<0.001	<0.001	<0.001
Cerebrovascular disease	131/998 (13.1) (11.0, 15.2)	22/229 (9.6)	44/404 (10.9)	65/363 (17.9)	0.004	0.612	0.006	0.006
Aortic aneurysm	24/1008 (2.4) (1.4, 3.3)	4/230 (1.7)	4/409 (1.0)	16/367 (4.4)	0.013	0.413	0.094	0.007
Peripheral vascular disease	198/1006 (19.7) (17.2, 22.1)	33/231 (14.3)	64/409 (15.6)	100/364 (27.5)	<0.001	0.645	<0.001	<0.001
Chronic obstructive pulmonary disease	229/1011 (22.7) (20.1, 25.2)	32/231 (13.9)	94/409 (23.0)	101 (27.4)	<0.001	0.006	<0.001	0.159
Creatinine clearance <20 mL/min	148/996 (14.9) (12.7, 17.1)	18/229 (7.9)	55/403 (13.6)	73/362 (20.2)	<0.001	0.031	<0.001	0.016
Atrial fibrillation	334/1006 (33.2) (30.3, 36.1)	63/231 (27.3)	135/409 (33.0)	134/364 (36.8)	0.056	–	–	–
Permanent pacemaker	131 (12.9) (10.8, 15.0)	22 (9.5)	48 (11.7)	61 (16.5)	0.028	0.397	0.016	0.050
Pulmonary hypertension	128/968 (13.2) (11.1, 15.4)	6/222 (2.7)	33/393 (8.4)	88/351 (25.1)	<0.001	0.008	<0.001	<0.001
Additional surgical history								
Porcelain aorta	41/1009 (4.1) (2.8, 5.3)	13/231 (5.6)	11/411 (2.7)	17/365 (4.7)	0.159	–	–	–
Liver cirrhosis	10/1012 (1.0) (0.4, 1.6)	9/231 (3.9)	0/411 (0.0)	1/368 (0.3)	0.002	0.014	0.008	0.459
Right ventricular insufficiency	41/1003 (4.1) (2.9, 5.3)	3/231 (1.3)	14/409 (3.4)	24/361 (6.6)	0.008	0.122	0.006	0.043
Prior thoracic burning sequelae	2/1013 (0.2) (0.0, 0.5)	0/232 (0.0)	1 (0.2)	1/367 (0.3)	0.996	–	–	–
Echocardiography								
Aortic valve area, cm^2	0.7 ± 0.3 (809) (0.7, 0.7)	0.7 ± 0.3 (180)	0.7 ± 0.3 (339)	0.7 ± 0.3 (288)	0.215	–	–	–
Peak aortic valve gradient, mmHg	75.9 ± 25.1 (881) (74.2, 77.5)	78.7 ± 26.2 (197)	78.8 ± 25.2 (363)	70.9 ± 23.5 (319)	<0.001	0.957	<0.001	<0.001
Mean aortic valve gradient, mmHg	45.6 ± 15.5 (903) (44.6, 46.6)	47.3 ± 15.8 (198)	47.4 ± 15.5 (374)	42.6 ± 14.9 (329)	<0.001	0.916	<0.001	<0.001
Left ventricular ejection fraction, %	53.3 ± 13.7 (873) (52.4, 54.2)	57.7 ± 11.5 (189)	55.7 ± 12.5 (361)	48.0 ± 14.4 (322)	<0.001	0.065	<0.001	<0.001
LV ejection fraction <35%	83/873 (9.5) (7.6, 11.5)	6/189 (3.2)	19/361 (5.3)	58/322 (18.0)	<0.001	0.269	<0.001	<0.001
Moderate or severe mitral regurgitation[g]	273/982 (27.8) (25.0, 30.6)	51/222 (23.0)	105/402 (26.1)	117/356 (32.9)	0.022	0.385	0.011	0.042
Moderate or severe tricuspid regurgitation[g]	177/916 (19.3) (16.8, 21.9)	22/204 (10.8)	60/371 (16.2)	95/339 (28.0)	<0.001	0.079	<0.001	<0.001

[a]Data are presented as means ± standard deviation (n) or n/total n (%) unless otherwise noted. 95% CIs are presented for data reported for all patients. Reported values are for all patients unless otherwise noted. General linear models and logistic regression models were used to test for overall and group pairwise differences. Pairwise comparison *P*-values should be compared with a Bonferroni-adjusted alpha level of 0.05/3 = 0.017.
[b]The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) measures patient risk at the time of cardiovascular surgery and is calculated by a logistic regression equation. Scores range from 0 to 100%, with higher scores indicating greater risk.
[c]*P*-values represent comparisons between the EuroSCORE ≤10% and EuroSCORE >10–20% groups.
[d]*P*-values represent comparisons between EuroSCORE ≤10% and EuroSCORE >20% groups.
[e]*P*-values comparisons between EuroSCORE >10–20% and EuroSCORE >20% groups.
[f]The Society of Thoracic score measures risk at the time of cardiovascular surgery on a scale from 0 to 100%, with higher numbers indicating greater risk.
[g]Moderate or severe mitral or tricuspid regurgitation was defined as regurgitation of Grade 3+ or higher.

Table 2 **Procedural characteristics for all patients and by EuroSCORE[a]**

	All patients ($n = 996$)	EuroSCORE[b] ≤10% ($n = 229$)	EuroSCORE >10–20% ($n = 406$)	EuroSCORE >20% ($n = 360$)	Overall *P*-value[c]
Procedural outcomes					
Successful vascular access, delivery and deployment of device, and successful retrieval of the delivery system	971/996 (97.5) (96.5, 98.5)	223/229 (97.4)	400/406 (98.5)	347/360 (96.4)	0.185
Correct position of one device in the proper anatomical position at the end of procedure[d]	983/996 (98.7) (98.0, 99.4)	225/229 (98.3)	405/406 (99.8)	352/360 (97.8)	0.113
Mean aortic valve gradient <20 mmHg	776/807 (96.2) (94.8, 97.5)	178/186 (95.7)	315/330 (95.5)	283/291 (97.3)	0.482
No severe aortic regurgitation	871/873 (99.8) (99.5, 100)	201/201 (100)	354/355 (99.7)	315/316 (99.7)	0.923
Only one valve used[d]	956/996 (96.0) (94.8, 97.2)	220/229 (96.1)	390/406 (96.1)	345/360 (95.8)	0.984
Procedural mortality[e]	5/996 (0.5) 0.1–0.9%	0/229 (0.0)	2/406 (0.5)	3/360 (0.8)	0.579
Balloon aortic valvuloplasty (BAV)					
Pre-implant BAV	906/996 (91.0) (89.2, 92.7)	207/229 (90.4)	379/406 (93.3)	319/360 (88.6)	0.073
Post-implant BAV	235/996 (23.6) (21.0, 26.2)	55/229 (24.0)	100/406 (24.6)	80/360 (22.2)	0.726
Major complications, valve related					
Annulus rupture	0/996 (0.0) (0.0, 0.0)	0/229 (0.0)	0/406 (0.0)	0/360 (0.0)	–
Valve embolization[d]	2/996 (0.2) (0.0, 0.5)	0/229 (0.0)	2/406 (0.5)	0/360 (0.0)	0.551
Conversion to surgical aortic valve replacement[f]	1/995 (0.1) (0.0, 0.3)	1/229 (0.4)	0/406 (0.0)	0/359 (0.0)	0.460
Coronary compromised[g]	1/887 (0.1) (0.0, 0.3)	0/197 (0.0)	0/364 (0.0)	1/325 (0.3)	0.746

[a]Data are presented as *n*/total *n* (%) (95% CI).
[b]The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) measures patient risk at the time of cardiovascular surgery and is calculated by a logistic regression equation. Scores range from 0 to 100%, with higher scores indicating greater risk.
[c]Logistic regression models were used to test for overall and group pairwise differences. Pairwise comparison *P*-values should be compared with a Bonferroni-adjusted alpha level of 0.05/3 = 0.017.
[d]Forty patients required use of a second CoreValve bioprosthesis (site-reported); 34 cases were due to malplacement of the first valve, of which 19 were due to valve insufficiency; and 6 cases were due to other reasons. In all cases the second CoreValve bioprosthesis was successfully implanted in the proper anatomical position.
[e]Two patients died from severe, diffuse haemorrhage without evidence of vascular perforation at autopsy, 1 patient died from a rupture of the aortic arch, 1 patient died of acute respiratory failure, and 1 patient died secondary to right heart failure as a result of acquired ventricular septum defect most likely due to the post-dilatation of the Medtronic CoreValve prosthesis with an oversized balloon.
[f]This patient had paravalvular regurgitation, which persisted in spite of correct transcatheter heart valve positioning and post-implant BAV. The AR did not improve, and based on the patient's clinical status, it was decided to implant a surgical valve.
[g]Patient had previous coronary artery bypass grafting; compromised flow in native vessel with good flow in grafts.

Table 3 Outcomes at 30-day follow-up for all patients and by EuroSCORE[a]

	All Patients ($n = 996$)	EuroSCORE[b] ≤ 10% ($n = 229$)	EuroSCORE >10–20% ($n = 406$)	EuroSCORE >20% ($n = 360$)	Log-rank *P*-value	*P*-value[c]	*P*-value[d]	*P*-value[e]
Primary endpoint								
MACCE (VARC)	8.0 (6.3, 9.7)	3.5	9.1	9.7	0.017	0.008	0.005	0.812
All-cause mortality	4.5 (3.2, 5.8)	2.6	4.4	5.8	0.193	–	–	–
Myocardial infarction (VARC)	0.2 (0.0, 0.5)	0.0	0.2	0.3	0.737	–	–	–
Emergent cardiac surgery or percutaneous reintervention	1.3 (0.6, 2.1)	0.4	1.3	2.0	0.283	–	–	–
Stroke (VARC)	3.0 (2.0, 4.1)	1.8	4.2	2.5	0.170	–	–	–
Additional VARC endpoints								
Cardiovascular mortality[f]	3.4 (2.3, 4.6)	1.7	3.5	4.5	0.218	–	–	–
Bleeding	29.0 (26.1, 31.9)	23.2	32.4	28.9	0.056	–	–	–
Life-threatening or disabling bleeding	4.0 (2.8, 5.3)	3.5	5.0	3.4	0.473	–	–	–
Major bleeding	9.7 (7.8, 11.6)	7.0	9.7	11.4	0.206	–	–	–
Minor bleeding	17.4 (15.0, 19.9)	15.8	20.1	15.6	0.208	–	–	–
Vascular complications[g]	20.7 (18.2, 23.3)	16.2	23.2	20.6	0.118	–	–	–
Major	10.9 (8.9, 12.8)	7.4	13.1	10.3	0.084	–	–	–
Minor	10.2 (8.2, 12.1)	9.2	10.1	10.9	0.805	–	–	–
Stroke or transient ischaemia attack	3.3 (2.2, 4.5)	1.8	5.0	2.5	0.053	–	–	–
Major stroke	1.2 (0.5, 1.9)	0.9	2.0	0.6	0.173	–	–	–
Minor stroke	1.8 (1.0, 2.7)	0.9	2.2	2.0	0.458	–	–	–
Transient ischaemia attack	0.4 (0.0, 0.8)	0.0	1.0	0.0	0.055	–	–	–
Acute kidney injury—stage III	0.4 (0.0, 0.8)	0.0	0.0	1.1	0.029	<0.001	0.109	0.033
Additional endpoints								
New pacemaker implantation	26.3 (23.5, 29.1)	29.0	26.1	24.8	0.511	–	–	–
Death from any cause or major stroke	5.1 (3.8, 6.5)	2.6	5.7	6.1	0.146	–	–	–

MACCE, major adverse cardiovascular and cerebrovascular events. VARC, Valve Academic Research Consortium.

[a]Data presented as Kaplan–Meier estimates and 95% CI using the Peto standard error. Log-rank tests were used to test for differences across and between groups. Pairwise comparison *P*-values should be compared with a Bonferroni-adjusted alpha level of 0.05/3 = 0.017.

[b]The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) measures patient risk at the time of cardiovascular surgery, and is calculated by a logistic regression equation. Scores range from 0 to 100%, with higher scores indicating greater risk.

[c]*P*-values represent comparisons between the EuroSCORE ≤10% and EuroSCORE >10–20% groups.

[d]*P*-values represent comparisons between EuroSCORE≤10% and EuroSCORE >20% groups.

[e]*P*-values comparisons between EuroSCORE 10–20% and EuroSCORE >20% groups.

[f]Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

[g]We observed 114 major vascular complication events in ADVANCE: vascular dissection (38), bleeding (22), vascular perforation (14), closure device failure (8), pseudoaneurysm (7), vessel occlusion (5), embolism or distal ischaemia (4), aortic rupture/dissection (4), access site/retroperitoneal hematoma (4), access site laceration (2), infection requiring surgery (2), access site rupture (1), and access site stenosis (1).

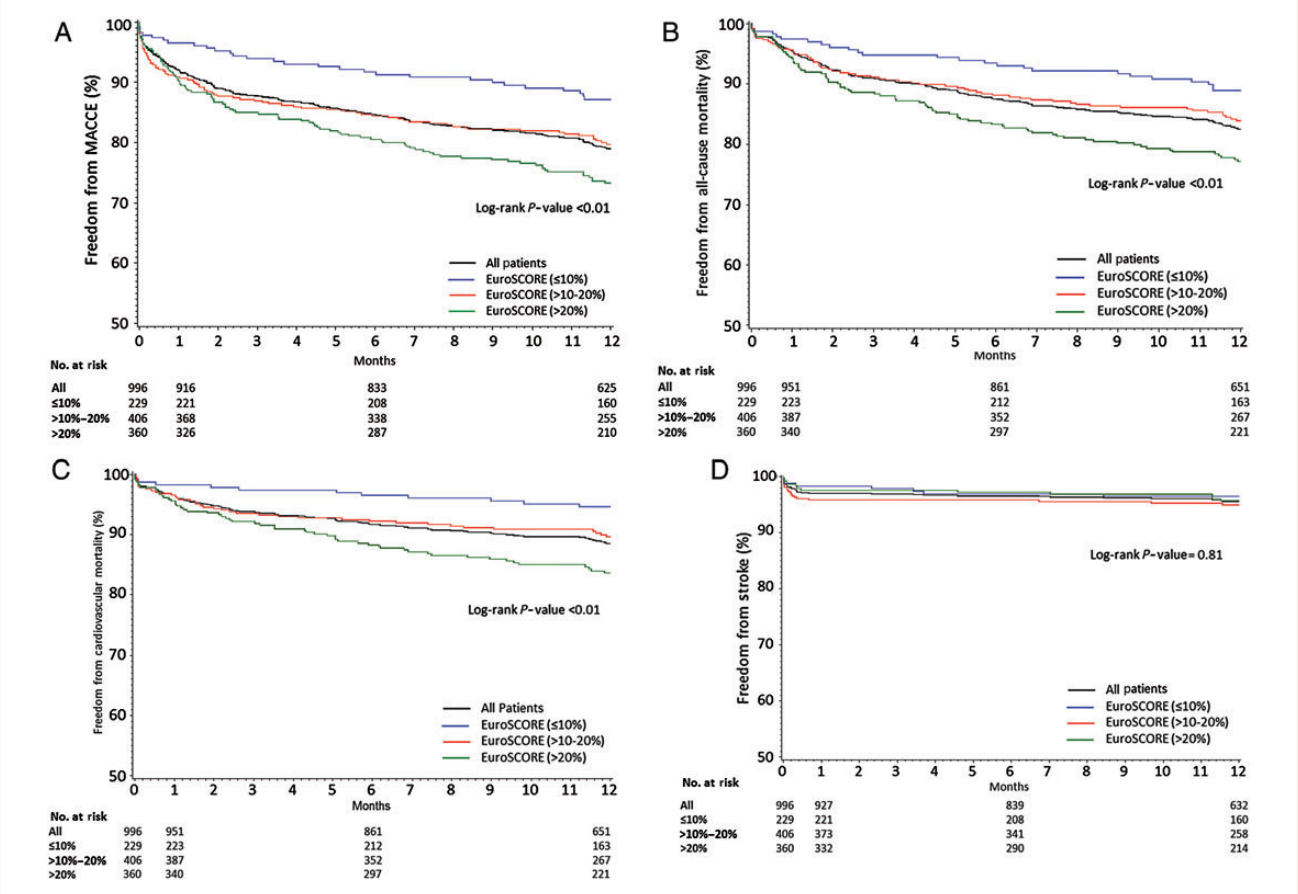

Figure 1 Kaplan–Meier time to event analyses for the primary select endpoints for all patients and according to logistic EuroSCORE (≤10%, >10–20%, and above 20%). (*A*) The rate of the primary endpoint of major adverse cardiovascular and cerebrovascular events among patients in the ADVANCE study; (*B*) rates of death from any cause; (*C*) rates of death from cardiovascular causes*; (*D*) rates of stroke*. *P*-values represent comparisons among the three EuroSCORE groups using the log-rank test. *Per VARC-1 definitions.[21]

months, a lower risk profile was associated with greater survival (*Table 4*).

Predictors of mortality

The predictors of mortality at 12 months are reported in *Table 5*. In the multivariable model, besides a low baseline mean gradient, the occurrence of kidney injury stage III and moderate-to-severe AR at discharge (*Figure 3*) was identified as significant independent predictors of mortality at 12 months.

Discussion

The CoreValve ADVANCE study shows that treatment of 'real-world' inoperable or high-risk patients suffering from aortic stenosis with the CoreValve System—by an experienced TAVI team—is safe and associated with an improvement in aortic valve function in the presence of low stroke and mortality rates at 30-day and 12-month follow-up. Compared with previously reported non-randomized registries, ADVANCE is a robust study with several unique features it is the largest, multi-centre, prospective CoreValve TAVI study; it is fully monitored and the primary endpoint-related events were adjudicated by an independent Clinical Event Committee and all cerebrovascular events were assessed by a neurologist according to VARC-1 definitions; hence, the results are extremely robust.[8,10,11,13,14,20]

Overall mortality at 30 days was only 4.5% and therefore, considerably lower than reported for patients treated with the CoreValve System in the recently published FRANCE 2, the Italian, Belgian, UK, or German Registries.[10,11,13,14,20] This discrepancy cannot be explained by differences in the risk profile given that the logistic EuroSCORE in our study is almost identical to that of the above-mentioned registries. However, they contain data from early TAVI experience, in which the inexperience of the operators regarding patient selection, valve implantation and management of complications might have driven the early mortality.[3–7,13–15,20]

Despite excellent procedural success, the rates of vascular and bleeding complications were higher in ADVANCE when compared with the above-mentioned registries.[10,11,13,14,20] This discrepancy might be *partially* explained by the following factors: we applied VARC-1 definitions to adjudicate ADVANCE study events, whereas some others did not. ADVANCE employed complete monitoring and adjudication of events by an independent Clinical Events Committee, which made it less likely that events were missed. However, in ADVANCE the higher major bleeding and vascular

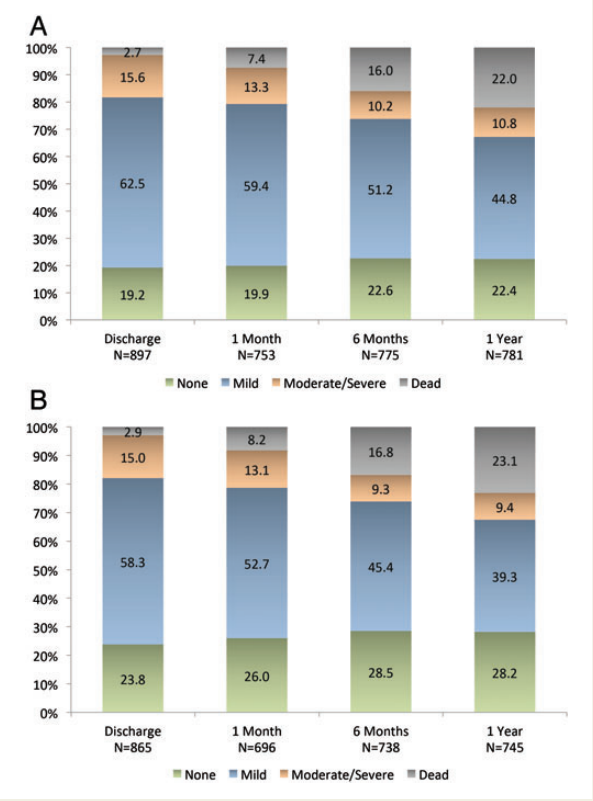

Figure 2 Aortic regurgitation at discharge, 30 days, 6 and 12 months determined by echocardiography. (*A*) Total aortic regurgitation by severity; moderate or severe aortic regurgitation was detected in 140 patients; two of these patients had snaring, which was successful in one. The other patient received a valve-in-valve procedure like two other patients, and in 62 out of the 140 patients a post-dilatation was performed to reduce the aortic regurgitation. Data are presented for all patients who had echocardiographic measurement of their aortic regurgitation at each time point and not as paired data sets for patients who had data at each time point. (*B*) Paravalvular regurgitation by severity.

complication rates compared with other studies might be also due to the fact that the methods to assess the access vessels size were left to the discretion of the operator. Moreover, the interventionalists were asked to follow the instructions for use of the CoreValve, which requires a minimal vessel diameter of 6 mm. Nevertheless, all of the commercially available sheaths are bigger than that and have an outer diameter of at least 7 mm. Especially in patients with circumferential calcification, aggressive advancement of the delivery sheath, which sometimes have a thicker shoulder at the tip, in a vessel that lost all its elasticity might have caused dissections, bleedings, and perforation. Careful assessment of the vasculature from the site of puncture up to the descending aorta is of utmost importance to prevent vascular and bleeding complications that are known to drive the mortality. This analysis should not be limited to the assessment of vascular size but should include amount and distribution of calcium as well as severity of kinking. Nevertheless, the mortality rate at 30 days was lower in ADVANCE when compared with other registries, which is consistent with the notion that the experience of the operators in ADVANCE to recognize and treat those complications might prevent a rise in early mortality. Moreover, the ADVANCE data underline that TAVI using the CoreValve System is in fact a remarkably safe procedure; there were no cases of annular rupture, only two cases of valve embolization, one case of conversion to conventional surgery and only one patient with a coronary compromise.

More than half of the implantations were performed with conscious sedation. This is indicative of an improved periprocedural management, where the valve size is selected based on pre-operative CT or TOE measurements, a greater confidence to judge the immediate results of TAVI only based on angiography and haemodynamics and to manage complications, even with the patients being awake. The reduced invasiveness of the procedure, especially the lack of mechanical ventilation might have its benefits particularly in patients with severe pre-existing pulmonary disease.

One feared complication of TAVI is stroke, since it is often associated with permanent disability. In ADVANCE, stroke rates were low at 30-day and 12-month follow-up. This is consistent with results from recent registries, and considerably lower when compared with first in man studies using the CoreValve System and the data from the PARTNER study.[11,16–20] Furthermore, <50% of strokes in our study were recognized during the first 2 days. This finding strongly suggests that procedural factors such as discontinuation of anticoagulants in patients with atrial fibrillation, new onset atrial fibrillation and athero- and thromboembolism from the ascending aorta or the arch might influence neurological outcome. Further studies are necessary to address these issues.

In the early days of TAVI, paravalvular leak was not attributed much significance. However, it has become clear that PVR is associated with reduced late survival.[14,18–20] These data are consistent with findings in the ADVANCE study, in which patients with moderate or severe PVR at hospital discharge had a cardiovascular mortality that was almost twice as high at 12 months when compared with those with none or only mild. All of these data, however, reinforce the need to reduce or eliminate paravalvular leaks in future device development, technological advances, and implant techniques.

The rate of Medtronic CoreValve embolization was 0.2% and therefore extremely low. On the contrary, almost 30% of the patients were implanted with a permanent pacemaker at 30 days due to conduction abnormalities, which is well in line with recent data from FRANCE 2 (24.2% after CoreValve System) and the UK (24.4% after CoreValve System), but lower than that reported in the German Registry (39%).[11,14,20] The reason for the occurrence of heart block after CoreValve System implantation is probably multifactorial involving patient and procedural factors.[22] It may well be that on one hand a deep Medtronic CoreValve position might have prevented embolizations of the valve into the ascending aorta but on the other hand lead to a higher rate of permanent pacemaker implantations. Nevertheless, recent data suggest that changing the implantation strategy to include a target implant depth of 4–6 mm for the CoreValve bioprosthesis in the left ventricular outflow tract might reduce the rate of permanent pacemaker implantation to ~10% in the absence of an excessive risk of valve embolization.[24] Hence, further studies are necessary to understand the association between implantation depths, transient and persistent rhythms disorders requiring pacemaker implantation.

Subanalyses such as that of the PARTNER study and the UK Registry suggest that long-term survival after TAVI is a function of the

Table 4 Outcomes at 12-month follow-up for all patients and by EuroSCORE[a]

	All Patients ($n = 996$)	EuroSCORE[b] ≤10% ($n = 229$)	EuroSCORE >10–20% ($n = 406$)	EuroSCORE >20% ($n = 360$)	Log-rank *P*-value	*P*-value[c]	*P*-value[d]	*P*-value[e]
Primary outcomes								
MACCE (VARC)	21.2 (18.4, 24.1)	12.8	20.6	27.1	<0.001	0.012	<0.001	0.047
All-cause mortality	17.9 (15.2, 20.5)	11.1	16.5	23.6	<0.001	0.064	<0.001	0.016
Myocardial infarction (VARC)	0.9 (0.2, 1.6)	0.5	1.1	1.0	0.728	–	–	–
Emergent cardiac surgery or percutaneous reintervention	1.6 (0.6, 2.5)	0.4	1.3	2.7	0.104	–	–	–
Stroke (VARC)	4.5 (2.9, 6.1)	3.6	5.1	4.4	0.613	–	–	–
Additional VARC endpoints								
Cardiovascular mortality	11.7 (9.4, 14.1)	5.4	10.7	16.8	<0.001	0.029	<0.001	0.019
Bleeding	32.0 (28.4, 35.6)	26.9	34.7	32.3	0.128	–	–	–
Life-threatening or disabling bleeding	4.9 (3.3, 6.6)	4.0	5.5	4.9	0.684	–	–	–
Major bleeding	11.2 (8.7, 13.6)	9.4	10.5	13.0	0.307	–	–	–
Minor bleeding	19.3 (16.3, 22.4)	17.6	21.5	18.1	0.336	–	–	–
Vascular complications	21.9 (18.7, 25.0)	18.0	24.1	21.5	0.210	–	–	–
Major	12.0 (9.5, 14.5)	8.9	14.3	11.2	0.119	–	–	–
Minor	10.3 (7.9, 12.6)	9.6	10.1	10.9	0.879	–	–	–
Stroke or transient ischaemia attack	6.1 (4.3, 7.9)	5.0	7.4	5.3	0.343	–	–	–
Major stroke	2.2 (1.1, 3.3)	1.8	2.6	2.1	0.694	–	–	–
Minor stroke	2.3 (1.1, 3.5)	1.8	2.5	2.3	0.822	–	–	–
Transient ischaemia attack	1.7 (0.7, 2.7)	1.4	2.5	0.9	0.292	–	–	–
Acute kidney injury—stage III	0.6 (0.0, 1.2)	0.5	0.0	1.5	0.041	0.196	0.247	0.017
Additional endpoints								
New pacemaker implantation	29.2 (25.6, 32.7)	32.9	29.1	26.8	0.338	–	–	–
Death from any cause or major stroke	18.4 (15.7, 21.1)	11.1	17.5	23.8	<0.001	0.031	<0.001	0.036

[a]Data presented as Kaplan–Meier estimates and 95% CI using the Peto standard error. Log-rank tests were used to test for differences across and between groups. Pairwise comparison *P*-values should be compared with a Bonferroni-adjusted alpha level of 0.05/3 = 0.017.
[b]The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) measures patient risk at the time of cardiovascular surgery, and is calculated by a logistic regression equation. Scores range from 0 to 100%, with higher scores indicating greater risk.
[c]*P*-values represent comparisons between the EuroSCORE ≤10% and EuroSCORE >10–20% groups.
[d]*P*-values represent comparisons between EuroSCORE ≤10% and EuroSCORE >20% groups.
[e]*P*-values comparisons between EuroSCORE >10–20% and EuroSCORE >20% groups.

Table 5 Predictors of all-cause mortality at 12 months

Variable	Alive (n = 822)	Dead (n = 174)	Univariable model	P-value	Multivariable model	P-value
Male	396/822 (48.2)	95/174 (54.6)	1.25 (0.93, 1.68)	0.146		
Diabetes mellitus	247/815 (30.3)	59/170 (34.7)	1.18 (0.86, 1.61)	0.316		
Coronary artery disease	465/819 (56.8)	109/174 (62.6)	1.25 (0.92, 1.70)	0.159		
Previous myocardial infarction	285/822 (34.7)	65/174 (37.4)	1.13 (0.83, 1.53)	0.448		
Previous percutaneous coronary intervention	248/813 (30.5)	62/173 (35.8)	1.24 (0.91, 1.69)	0.179		
Previous coronary artery bypass	176/818 (21.5)	35/174 (20.1)	0.92 (0.63, 1.33)	0.644		
Cerebrovascular disease	25/822 (3.0)	18/174 (10.3)	3.02 (1.86, 4.93)	<0.001	1.84 (0.87, 3.85)	0.11
Peripheral vascular disease	152/815 (18.7)	44/172 (25.6)	1.43 (1.02, 2.02)	0.039	1.34 (0.86, 2.08)	0.20
Chronic obstructive pulmonary disease	178/818 (21.8)	48/174 (27.6)	1.31 (0.94, 1.83)	0.112		
Creatinine (mg/dL)	1.2 ± 0.7 (815)	1.5 ± 0.9 (173)	1.25 (1.12, 1.39)	<0.001	1.15 (0.99, 1.33)	0.06
Baseline New York Heart Association III/IV	644/822 (78.3)	139/174 (79.9)	1.09 (0.75, 1.58)	0.655		
Logistic EuroSCORE	18.6 ± 11.7 (822)	22.8 ± 14.2 (173)	1.02 (1.01, 1.03)	<0.001	1.01 (1.00, 1.03)	0.09
Baseline left ventricular ejection fraction ≤50%	255/707 (36.1)	67/148 (45.3)	1.44 (1.04, 1.99)	0.028	1.11 (0.72, 1.70)	0.64
Baseline mean aortic valve gradient	46.3 ± 15.9 (732)	42.2 ± 13.3 (153)	0.98 (0.97, 0.99)	0.003	0.99 (0.97, 1.00)	0.03
Transfemoral	730/822 (88.8)	150/174 (86.2)	0.81 (0.52, 1.24)	0.326		
Major vascular complication	89/822 (10.8)	32/174 (18.4)	1.75 (1.19, 2.57)	0.004	1.00 (0.54, 1.85)	0.99
Minor vascular complication	87/822 (10.6)	15/174 (8.6)	0.81 (0.48, 1.38)	0.447		
Life-threatening bleeding	31/822 (3.8)	17/174 (9.8)	2.57 (1.56, 4.24)	<0.001	2.04 (0.93, 4.44)	0.07
Major bleeding	89/822 (10.8)	24/174 (13.8)	1.25 (0.81, 1.93)	0.302		
Minor bleeding	166/822 (20.2)	26/174 (14.9)	0.72 (0.47, 1.09)	0.115		
Acute kidney injury (stage III)	0/822 (0.0)	6/174 (3.4)	10.97 (4.83, 24.92)	<0.001	9.75 (3.68, 25.84)	<0.001
New pacemaker	242/822 (29.4)	47/174 (27.0)	0.89 (0.64, 1.24)	0.482		
Discharge aortic regurgitation moderate/severe	111/743 (14.9)	29/130 (22.3)	1.62 (1.07, 2.44)	0.023	1.63 (1.03, 2.59)	0.04

All data reported as n/total n (%), means ± standard deviation (n) and hazard ratios (95% CI). Univariable predictors significant at $P \leq 0.05$ were included in the multivariable model.

pre-operative risk profile as indicated by logistic EuroSCORE or the STS score.[11,16–19] To understand the importance of the pre-operative risk profile on an outcome, we performed a subanalysis of ADVANCE and divided the study population in three groups according to the logistic EuroSCORE: ≤10%, >10% and ≤20% and >20%. At 30 days, the mortality rates among the three groups did not differ significantly. However, between 30 days and 12 months, the decline in survival was 8.5, 12.1, and 17.8% in those with a logistic EuroSCORE ≤10%, >10% and ≤20%, and >20%, respectively and was of cardiovascular origin in 21, 36, and 40% of the cases. These data are consistent with the notion that over the long term, patients with a high baseline logistic EuroSCORE continue to die from cardiovascular causes despite normalization of the aortic valve gradient, as well as from non-cardiovascular causes.

Nevertheless, in ADVANCE the mortality rate at 12 months is generally low (17.9%), including the subset of patients with a logistic EuroSCORE >20% (mean logistic EuroSCORE 32.3 ± 11.0%, 12-month mortality 23.6%) when compared with other registries or the PARTNER study (TAVI group; logistic EuroSCORE 26.4 ± 17.2%, 12-month mortality, 30.7%: standard medical therapy; logistic EuroSCORE 30.4 ± 19.1%, 12-month mortality, 49.7%), suggesting that TAVI using the CoreValve System by an experienced team is associated with a favourable outcome also in extreme-risk patients.[16–19]

The ADVANCE study has limitations: the total number of TAVI cases performed at the centres was larger than the number of patients that entered the ADVANCE study and some received other transcatheter valves. This was due to anatomical factors, decision of the patients, and the physician. Therefore, like in any other trial, we cannot exclude that a selection bias may have influenced the results and we are unable to report data from these patients treated outside of the ADVANCE study. In addition, the evaluation of AR by echo post-procedure was performed locally in the absence of a central echo core laboratory, which might have induced bias as well. About 25% of the patients had a logistic EuroSCORE <10% but were considered at high operative risk by the Heart Team consisting of a cardiologist and cardiac surgeon. It is highly likely that factors such as frailty, the presence of porcelain aorta or hostile chest—all factors not captured by the logistic EuroSCORE—convinced the Heart Team to propose a TAVI in these patients. This is supported by the finding that the presence of liver disease was more frequent in the group of patients with the lowest EuroSCORE. However, future trials such as Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI, ClinicalTrials.gov identifier; NCT01586910) are required to assess the results of TAVI in an intermediate risk cohort of patients with symptomatic aortic stenosis. However, ADVANCE was not a randomized trial and cases were selected by a Heart Team, and while comparisons

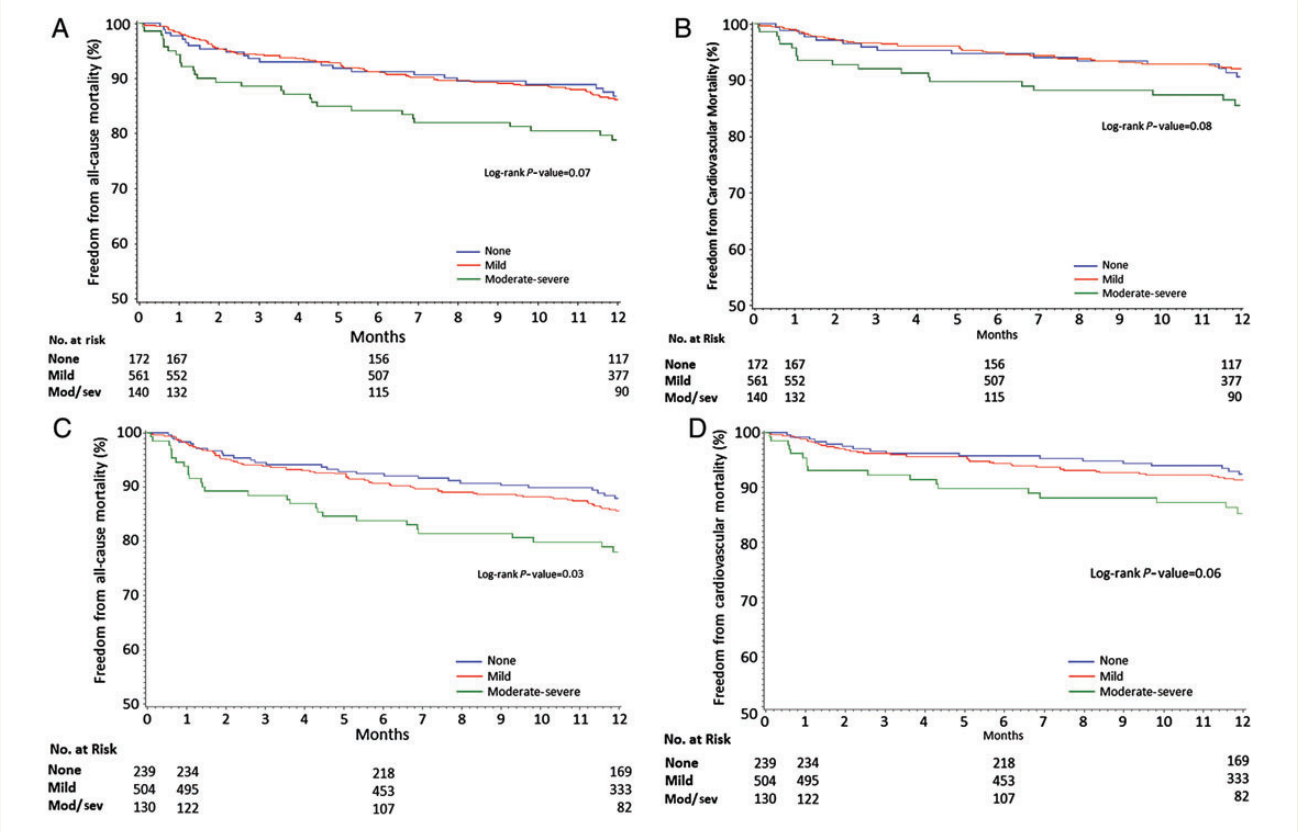

Figure 3 Time to event curves by severity of aortic regurgitation at discharge by echocardiography for select endpoints. (*A*) All-cause survival from any cause by aortic regurgitation (none vs. mild vs. moderate and severe); (*B*) cardiovascular survival by aortic regurgitation (none vs. mild vs. moderate); (*C*) all-cause survival by aortic regurgitation secondary to paravalvular leak (none vs. mild vs. moderate and severe as), (*D*) cardiovascular survival secondary to paravalvular aortic regurgitation (none vs. mild vs. moderate and severe). Pairwise log-rank testing showed that patients with mild paravalvular aortic regurgitation had similar survival to patients with no paravalvular regurgitation ($P = 0.30$), but worse survival compared with those with moderate and severe paravalvular regurgitation ($P = 0.04$).

to randomized trials may not be valid, this study does reflect expert clinical practice in real-world patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

Jane Moore, MS, ELS, a Medtronic employee, provided copyediting assistance and prepared all tables and figures. Shuzhen Li, PhD, also a Medtronic employee, and Stacia Kraus, MPH (NAMSA, Minneapolis, MN, USA) performed all statistical analyses for this report and ensure the accuracy of the data presented. Francesca Barbieri, MD, Rijk de Jong, MSc, and Maarten Hollander, MSc from Medtronic Bakken Research Center (Maastricht, The Netherlands) were responsible for overall study management.

Authors' contributions

A.L. conceived and designed the research, acquired the data, analysed, and interpreted the data, handled funding and supervision and drafted the manuscript. P.W., U.G., C.T., J.B., and S.Br. acquired the data, analysed and interpreted the data and drafted the manuscript. S.B., D.B., U.S., R.M., H.S., L.S., S.K., R.H., D.T., A.C., V.M.L., F.B., P.P., G.S., D.M., C.E., C.F., P.B., S.W., F.W.M., F.W., R.L., and R.B. acquired the data and made critical revision of the manuscript for important intellectual content.Dominique Himbert, MD, Bichat Hospital, Paris, France; Peter Crean, MD, St James's Hospital, Dublin, Ireland; José L. Pomar, MD, Hospital Clinic University of Barcelona, Barcelona, Spain, and Adam Witkowski, MD, Institute of Cardiology, Warsaw, Poland served as the Clinical Events Committee.

Funding

Medtronic, Inc. sponsored the ADVANCE study.

Conflict of interest: This included participating in trial design, managing data collection and validation, and performing all statistical analyses. The ADVANCE Steering Committee designed the study and had oversight of study activities. All authors had full access to the study data, and reviewed and approved the final version of the manuscript. The corresponding author had final responsibility for the decision to submit this manuscript for publication. Medtronic funded the Clinical Events Committee and core laboratory for ECG and angiographic analyses. A.L. has received

from Medtronic consultant fees as well as study-related travel expenses and lecture fees from Medtronic, St Jude Medical, and Biosensors. P.W. has received consultant fees from Medtronic, Edwards Lifesciences, and Biotronic; and remuneration for study-related travel and for developing education materials from Medtronic. U.G. has received consultant and lecture fees and study-related travel expenses from Medtronic and Edwards Lifesciences, and serves as a proctor for Medtronic; J.B. serves as a proctor for Medtronic; S.B. serves as a consultant to Medtronic and as a proctor for Medtronic and JenaValve and has received travel expenses from Edwards Lifesciences, Medtronic and Johnson & Johnson; D.B. has received consultant fees from Medtronic; U.S. serves as a proctor for Medtronic; H.S. has received honoraria and travel expenses from Medtronic, Edwards Lifesciences, HLT, JenaValve, and Venus; L.S. serves as a proctor for Medtronic; V.L. serves as a proctor for Medtronic; F.B. has received consultant fees from Medtronic; S.W. has received speaker fees from Abbott, AstraZeneca, Biosensors, Biotronik, Boston Scientific, Edwards Lifesciences, Eli Lilly, and Medtronic; S.W.'s institution has received research grants from Abbott, Biosensors, Biotronik, Boston Scientific, Cordis, Edwards Lifesciences, Medtronic, and St Jude Medical; R.L. has received consultant fees as well as study-related travel expenses, and has served as a proctor for Medtronic. In addition, R.L. has a patent-related relationship with Medtronic that is outside of the scope of this paper; R.B. serves as a proctor for Medtronic, and serves as a proctor and has received consultant fees from JenaValve; and SBr has received consultant fees from Medtronic, and consultant fees from St Jude Medical. C.T., R.M., S.K., R.H., D.T., P.L., A.C., G.S., D.M., C.E., C.F., P.B., F.M., and F.W. have nothing to disclose.

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CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehu266
Online publish-ahead-of-print 30 June 2014

Valve-in-valve transfemoral TAVR: Sapien 3 valve within a failed core valve bioprosthesis

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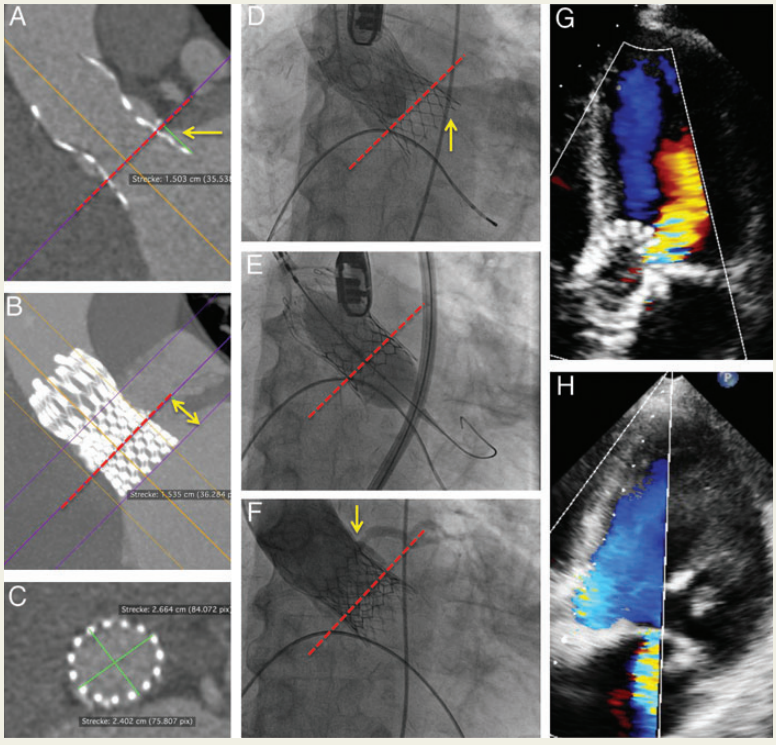

A 76-year-old woman with a medical history of stroke, hypertension, and paroxysmal atrial fibrillation presented with symptoms of acute decompensated heart failure 1.5 years after undergoing transcatheter aortic valve replacement (TAVR) with a bioprosthetic Medtronic Core Valve (CoV) for severe aortic stenosis. Her echocardiogram showed an ejection fraction of 33% with severe paravalvular aortic insufficiency (AI).

The longitudial CT image (*Panel A*) shows a 29 mm CoV implanted 15 mm below the annulus (red line); Therefore, the CoV skirt does not cover the annulus along the left coronary cusp region (arrow). The CoV skirt is 3 mm below the annulus and 12 mm from the distal edge (*Panel B*). The transverse CT image shows an inadquately deployed CoV (*Panel C*). The high degree AI jet through the paravalvular gap (arrow) was also noted on angiography (*Panel D*). A 26 mm Sapien 3 (S3) valve was deployed with placement of its outer skirt above the CoV gap (*Panel E*). The S3 valve was placed slightly below the left main (LM) to avoid a double stent layer at the LM coronary ostium (*Panel F*). The high degree, eccentric AI (*Panel G*) as noted on echo before the S3 valve implant was successfully reduced to an insignificant AI (*Panel H*) post-procedure.

The feasibility of valve-in-valve (VIV) TAVR for the treatment of failed AV prosthesis has been described before. Here, for the first time, we demonstrate a sussessful VIV TAVR procedure using the new generation Sapien 3 valve.

A.M.K. is a medical consultant for and receives research support from Edwards Life Sciences. The other authors have no conflict of interest to disclose.